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Proposed Registration Decision PRD2013-07

Metrafenone

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Overview

Proposed Registration Decision for Metrafenone

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Metrafenone Technical Fungicide and Vivando SC Fungicide, containing the technical grade active ingredient metrafenone, to control powdery mildew on grapes.

Metrafenone Technical Fungicide (Registration Number 29764) and Vivando SC Fungicide (Registration Number 29765) are conditionally registered in Canada. The detailed review for Metrafenone Technical Fungicide and Vivando SC Fungicide can be found in Evaluation Report ERC2011-10, *Metrafenone*. The current applications were submitted to convert Metrafenone Technical Fungicide and Vivando SC Fungicide from conditional registration to full registration.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Metrafenone Technical Fungicide and Vivando SC Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on metrafenone, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision[4] on metrafenone, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation section of this consultation document.

What Is Metrafenone?

Metrafenone is a benzophenone fungicide with protectant and curative properties for the control of powdery mildew (*Uncinula necator*) on grapes.

Health Considerations

Can Approved Uses of Metrafenone Affect Human Health?

Potential exposure to metrafenone may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when metrafenone products are used according to label directions.

In laboratory animals, the technical grade active ingredient is of low acute oral, dermal and inhalation toxicity; is non-irritating to the skin, not a dermal sensitizer and minimally irritating to the eyes. The end-use product, Vivando SC Fungicide, is of low acute oral, dermal and inhalation toxicity; is non-irritating to the skin and not a sensitizer. The end-use product is mildly irritating to the eyes. Consequently, the signal words "CAUTION – EYE IRRITANT" are required on the label of the end-use product.

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[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.
[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Metrafenone was not genotoxic and not likely to pose a carcinogenic risk to humans. There was also no indication that metrafenone caused damage to the nervous system. Common effects of toxicity in animals given daily doses of metrafenone over longer periods of time were changes to the kidneys and liver, irritation to the ear, and effects on the blood indicative of regenerative anaemia.

When metrafenone was given to pregnant animals, effects on the developing fetus, such as decreased body weight compared to controls and an increase in early fetal loss, were only observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to metrafenone than the adult animal.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and children 1–2 years old, the subpopulation that would ingest the most metrafenone relative to body weight, are expected to be exposed to less than 2% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from metrafenone is not of concern for all population sub-groups.

Animal studies revealed no acute health effects. Consequently, a single dose of metrafenone is not likely to cause acute health effects in the general population (including infants and children).

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

The analytical methodology data submitted to support the conversion from conditional to full registration are adequate. For the MRLs for this active ingredient, please refer to the Science Evaluation section of ERC2011-10, *Metrafenone*.

Occupational Risks From Handling Vivando SC Fungicide

Occupational risks are not of concern when Vivando SC Fungicide is used according to the label directions, which include protective measures.

Farmers and pesticide applicators who mix, load or apply Vivando SC Fungicide as well as field workers entering freshly treated fields can come in direct contact with Vivando SC Fungicide residues on the skin or through inhalation of spray mists. Therefore, the label specifies that anyone mixing/loading and applying Vivando SC Fungicide must wear long sleeved shirt, long

pants, chemical resistant gloves, socks and footwear. The label also requires that workers do not enter treated fields for four days after application to perform girdling or cane turning and 12 hours for all other postapplication activities. Taking into consideration these label statements, the number of applications and the expectation of the exposure period, risks for farmers and applicators are not a concern.

For bystanders, exposure is expected to be much less than that of field workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Metrafenone Is Introduced Into the Environment?

Metrafenone enters the environment when used as a fungicide on grape crops. Metrafenone is toxic to some non-target aquatic organisms. It is persistent in aerobic soil and is expected to carryover. Metrafenone is not persistent in anaerobic soil or in water, and it does not form any transformation products of environmental concern. Metrafenone is not expected to reach groundwater. Label instructions including spray buffer zones are required during pesticide application and handling.

Metrafenone is persistent in the terrestrial environment and displays low soil mobility. Based on field studies, approximately 40–45% carryover into the next growing season may be expected in soil. Metrafenone is sparingly soluble in water and is stable to hydrolysis. Despite these characteristics, it is not persistent in the aquatic environment. Many minor transformation products are formed, however, they do not pose an environmental concern because they are transient in nature and their concentrations are low. Due to low volatility (volatile organic compounds were not detected in the volatility traps used in laboratory incubation studies), metrafenone residues are not expected in the air, nor is long-range aerial transport expected. Leaching to groundwater is not a concern for metrafenone. It is not expected to bioaccumulate. Specific instructions to prevent soil carryover into the next growing season and runoff into aquatic habitats are provided on the end-use product label.

Metrafenone poses a negligible risk to the non-target terrestrial invertebrates tested including earthworms, honeybees, and beneficial arthropods. It also poses a negligible risk to the terrestrial vertebrates tested, including birds and small mammals. Although it displays low toxicity to terrestrial plants, there is some uncertainty regarding risk to plants owing to low application test rates. For freshwater organisms inhabiting waters close to 1 m in depth (80 cm deep or greater), metrafenone poses a negligible risk to all species tested. These include daphnids, chironomids, cold water fish (juvenile and early life stages), warm water fish (juvenile life stages), green algae, blue green algae, diatoms and aquatic vascular plants. However, metrafenone may pose an acute and chronic risk to amphibians inhabiting shallow waters (15 cm or less in depth). On an acute basis, metrafenone poses a negligible risk to estuarine/marine species including mysid shrimp, eastern oyster, and marine algae (represented by diatoms). It may pose a risk to marine fish (represented by sheepshead minnow) on an acute basis. On a chronic basis, it may pose a risk to mysid shrimp. Although the level of concern was exceeded for amphibians (acute and

chronic), sheepshead minnow (acute), and mysid shrimp (chronic), proposed precautionary measures including label statements and spray buffer zones (1–2 m in size) are expected to adequately mitigate risk resulting from drift of metrafenone into the habitats of these sensitive organisms.

Value Considerations

What Is the Value of Vivando SC Fungicide?

Vivando SC Fungicide is a broad spectrum fungicide with strong activity against powdery mildew.

Vivando SC Fungicide is to be used to control powdery mildew on grapes. There are several alternative modes of action registered for control of this disease, two of which are strobilurin fungicides, with high risk of development of pest resistance. Metrafenone has a different mode of action which will aid in resistance management when used as a component in a fungicide spray program.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Vivando SC Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Vivando SC Fungicide on the skin, anyone mixing, loading and applying Vivando SC Fungicide must wear a long sleeved shirt, long pants, chemical resistant gloves, socks and footwear during mixing/loading, application, clean-up and repair.

Environment

No new risk-reduction measures are required for the environment as a result of the new data submitted for the full registration of metrafenone and its associated end-use product. Refer to ERC2011-10, *Metrafenone* for a full list of environmental risk-reduction measures required on product labels.

Next Steps

Before making a final registration decision on metrafenone, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on metrafenone (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Metrafenone

1.0 The Active Ingredient, Its Properties and Uses

Please refer to Evaluation Report ERC2011-10, *Metrafenone*, for details on the active ingredient, the end-use product and their properties.

1.1 Directions for Use

To control powdery mildew (*Uncinula necator*) in grapes, Vivando SC Fungicide should be applied at 0.750 L per hectare (224 g active ingredient (a.i.) per hectare) up to six times at 14–21 day intervals. For more information regarding application timing, see ERC2011-10, *Metrafenone*.

1.2 Mode of Action

Metrafenone inhibits growth of mycelium on the leaf surface, leaf penetration, formation of haustoria and sporulation.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Metrafenone Technical Fungicide have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

Analytical methods using high-performance liquid chromatography with mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

Please refer to ERC2011-10, *Metrafenone* for previously reviewed data on residue analytical methodology.

To take advantage of advances in sample clean-up and detection techniques, the multiresidue QuEChERS method was adapted as a high performance liquid chromatography method with tandem mass spectrometry (HPLC-MS/MS) for the determination of metrafenone, and proposed for enforcement purposes in plant commodities. This method fulfilled the requirements with regards to specificity, accuracy and precision at the limit of quantitation of the method. Acceptable recoveries (70–120%) were obtained in plant matrices. The method was successfully validated by an independent laboratory on wheat (forage, straw, grain), cucumber, lemon, beans (dried seed), oilseed rape (seed) and hops (dried cones). Adequate extraction efficiencies were demonstrated using radiolabelled cucumber samples analyzed with the enforcement method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

In the original review for registration as detailed in ERC2011-10, *Metrafenone*, there were indications of possible immunotoxicity occurring in the 2-generation reproductive toxicity study which included haematological changes such as decreases in leukocytes and differential white blood cell counts in adult and offspring females of all generations and male F_1 adults and F_2 pups. As a result, an immunotoxicity study was requested and submitted by the applicant. The study found no treatment-related effects on the spleen or thymus. While there were serious limitations in the immunotoxicity functional assay that undermines the sensitivity of the study, based on the lack of effect in the associated immune system organs at any dose level tested, it was determined that any adverse effects on the immune system would occur at doses much higher than other effects observed in the rest of the database. Further, there are no changes indicative of immunotoxicity in the rest of the database and the current endpoints are protective of any potential immune effects. The overall weight of evidence indicates that there are no serious effects on the immune system at the doses tested. Consequently, the 3-fold factor for database deficiency has been removed. The toxicological endpoints for human health risk assessment are summarized in Appendix I, Table 3.

Incident Reports

Since 26 April 2007 registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of the Health Canada website at healthcanada.gc.ca/pmra. Incidents from Canada and the United States were searched and reviewed for active metrafenone. As of 30 January 2013, there were no incident reports submitted to the PMRA for products containing metrafenone.

3.1.1 *Pest Control Products Act* Hazard Characterization

The submitted data did not impact the PCPA factor as outlined in ERC2011-10, *Metrafenone*.

3.2 Occupational and Residential Risk Assessment

Please refer to ERC2011-10, *Metrafenone* for a detailed evaluation of occupational and residential risk from the use of Vivando SC Fungicide.

3.3 Food Residues Exposure Assessment

3.3.1 Residues in Plant and Animal Foodstuffs

Please refer to ERC2011-10, *Metrafenone* for a summary of the previously reviewed data and the rationale for the regulatory decision. The information captured herein only relates to the analytical methodology data provided to the PMRA in support of the conversion from conditional to full registration, and the change in the chronic dietary exposure results due to the revised acceptable daily intake (ADI).

The analytical methodology data requirements identified in ERC2011-10, *Metrafenone* were submitted and deemed to be adequate. The data demonstrate that the submitted analytical methodology is acceptable.

3.3.2 Dietary Risk Assessment

Chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.3.2.1 Chronic Dietary Exposure Results and Characterization

The following inputs were used in the refined chronic analysis: median residues from grape field trial data, and experimental processing factors for juice, wine and raisins. It was assumed that 100% of crops were treated. Residue inputs were adjusted to account for potential exposure to unknown metabolites. The refined chronic dietary exposure from all supported metrafenone food uses (alone) for the total population, including infants and children, and all representative population subgroups is below 2% of the ADI. Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to metrafenone from food and water is 0.3% of the ADI (0.000815 mg/kg bw/day) for the total population. The highest exposure and risk estimate is for children 1–2 years old at 1.6% of the ADI (0.003926 mg/kg bw/day).

3.3.2.2 Acute Dietary Exposure Results and Characterization

Please refer to ERC2011-10, *Metrafenone*. As no relevant acute toxicological endpoints were identified, an acute dietary assessment was not required.

3.3.3 Aggregate Exposure and Risk

Please refer to ERC2011-10, *Metrafenone*. The aggregate risk for metrafenone consists of exposure from food and drinking water sources only; there are no residential uses.

3.3.4 Maximum Residue Limits

Please refer to ERC2011-10, *Metrafenone* for the MRLs for metrafenone as well as the nature of the residues in plant matrices and field trial data. The chronic dietary risk estimates are summarized in Appendix I, Table 4.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Refer to Evaluation Report ERC2011-10, *Metrafenone* for a full description of the fate and behaviour of metrafenone in the environment.

For conversion from conditional to full registration, the registrant provided a data clarification report as an amendment to the original study of aerobic biotransformation in water-sediment system. A review of the report determined that all unidentified transformation products were present at concentrations below 5% of applied. Therefore, the submitted data supported the conclusion in the original study that no major transformation product was produced in the aerobic water-sediment environment.

4.2 Environmental Risk Characterization

Refer to ERC2011-10, *Metrafenone* for a full description of the environmental risk characterization for metrafenone and its associated end-use product.

The data submitted for the conversion do not affect environmental fate parameters and ecotoxicity endpoints. Therefore, there is no change to the environmental risk assessment.

5.0 Value

5.1 Effectiveness Against Pests

5.1.1 Acceptable Efficacy Claims

Efficacy data submitted were sufficient to support the claim of control of powdery mildew on grapes at a rate of 0.75 L/ha. Results of the review of efficacy data and value information can be found in Evaluation Report ERC2011-10, *Metrafenone*.

5.2 Sustainability

5.2.1 Survey of Alternatives

The chemical fungicides listed in Appendix I, Table 5 are registered for control of powdery mildew (*Uncinula necator*) on grapes.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

Please refer to Evaluation Report ERC2011-10, *Metrafenone* for information on Toxic Substances Management Policy Considerations.

6.2 Formulants and Contaminants of Health or Environmental Concern

Please refer to ERC2011-10, *Metrafenone* for information on formulants and contaminants of health or environmental concerns.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for metrafenone is adequate to define the majority of toxic effects that may result from exposure to metrafenone. In subchronic and chronic studies on laboratory animals, the primary targets were body weight, the liver, kidney, ears and changes to the haematology parameters indicative of regenerative anaemia. The available evidence is that metrafenone does not pose a carcinogenic risk and metrafenone is not considered a neurotoxicant. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies.

Mixers, loaders and applicators handling Vivando SC Fungicide and workers entering treated areas are not expected to be exposed to levels of metrafenone that will result in an unacceptable risk when Vivando SC Fungicide is used according to label directions. The personal protective equipment on the product label is adequate to protect chemical handlers and the restricted-entry intervals are adequate to protect workers entering treated fields.

The nature of the residue in grapes is adequately understood. The residue definition for enforcement of maximum residue limits is metrafenone. The proposed use of metrafenone on grapes does not constitute an unacceptable chronic dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits to protect human health. The PMRA recommends that the following maximum residue limits be specified for residues of metrafenone: 4.5 ppm in/on grapes, 17 ppm in/on raisins. Residues in juice and wine will be covered by the 4.5 ppm maximum residue limit for grape raw agricultural commodities.

7.2 Environmental Risk

Refer to Evaluation Report ERC2011-10, *Metrafenone* for a full description of the environmental risks of metrafenone and its associated end-use product.

Additional data supplied for this submission to convert from conditional to full registration supported the conclusion in the original study that no major transformation product was produced in the aerobic water-sediment environment. Therefore, the new data do not alter the original environmental risk profile for metrafenone.

7.3 Value

The data submitted to support Vivando SC Fungicide were adequate to demonstrate efficacy against powdery mildew (*Uncinula necator*) on grapes. No additional information was required.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Metrafenone Technical Fungicide and Vivando SC Fungicide, containing the technical grade active ingredient metrafenone, to control powdery mildew on grapes.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
a.i.	active ingredient
ADI	acceptable daily intake
bw	body weight
CAF	composite assessment factor
cm	centimetre(s)
DEEM-FCID	Dietary Exposure Evaluation Model
F_1	first generation
F_2	second generation
g	gram(s)
ha	hectare(s)
HPLC	high performance liquid chromatography
kg	kilogram(s)
L	litre(s)
LOAEL	lowest observed adverse effect level
LOQ	limit of quantitation
m/z	mass-to-charge ratio of an ion
m	metre(s)
mg	milligram(s)
MOE	margin of exposure
MRL	maximum residue limit
MS/MS	tandem mass spectrometry
NOAEL	no observed adverse effect level
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
QuEChERS	quick, easy, cheap, effective, rugged and safe
SC	soluble concentrate

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	MS-MS transition monitored	LOQ	References
Soil Sediment	M3441	Parent (CL 375839)	HPLC-MS/MS	411 m/z (quantitation) 411 – 228.0 (confirmation) 409 – 209.0 (confirmation)	5 ppb	1620207 1620206
		CL 377160		395, 397 (quantitation) 395 – 195.0 (confirmation) 397 – 195 (confirmation)		
Water (surface and drinking)	M3503	Parent	HPLC-MS/MS	411 m/z (quantitation) 411 – 229.1 (confirmation) 411 – 209.1 (confirmation)	0.05 ppb	1620208
		CL 375816		243 m/z (quantitation) 243 – 198.8 (confirmation)		
Plants	QuEChERS multiresidue method {Enforcement method}	Metrafenone	HPLC-MS/MS (high performance liquid chromatography with tandem mass spectrometry)		0.01 ppm Wheat (forage, straw, grain), cucumber, lemon, dried beans, rapeseed, hops (dried cones)	2104357 2266396 2266393

Table 2 Toxicity Profile of Technical Metrafenone*

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to body weights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Immunotoxicity Wistar rats PMRA 2179989	Immunotoxicity NOAEL: 12000 ppm (1086 mg/kg bw/day) Immunotoxicity LOAEL: not established Systemic NOAEL: 1000 ppm (80 mg/kg bw/day) Systemic LOAEL: 4000 ppm (315 mg/kg bw/day), based on liver weight increases

*This Table includes the additional requested study only, for the original toxicity profile table see Evaluation Report ERC2011-10 – *Metrafenone*.

Table 3 Toxicology Endpoints for Use in Health Risk Assessment for Metrafenone

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute Dietary	NONE		
	Acute reference dose = NONE		
Repeated Dietary	2-year rat toxicity study	increased blood loss in females, increased clotting times in males, extensive hepatotoxicity including adenomas in females, nephrotoxicity, metaplasia of the uterus and changes to the ears including chronic inflammation and cartilage hyperplasia in females	100
	Acceptable daily intake = 0.25 mg/kg bw/day		
Short-term Dermal and Inhalation[2]	rabbit developmental toxicity study	based on decreased body weight gain; decreased gravid uterine weights; decreased food consumption; increased red vaginal discharge; increased liver weights and increased general, diffuse and periportal hepatocellular hypertrophy, hepatocellular vacuolation	100
Intermediate-term Dermal[2]	rat multi-gen reproductive toxicity study	based on increased aggressive behaviour, vocalization, red material around nose – P♂; decreased body weights – F_1♂; decreased neutrophils, eosinophils, basophils – P♀; decreased leukocytes, lymphocytes – F_1♀; increased liver/brain weights – F_1♀ and decreased relative thymus weights – P♂	100

[1] CAF (composite assessment factor) refers to a total of uncertainty and PCPA factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2]Since an oral NOAEL was selected, a dermal absorption factor 19% was used in a route-to-route extrapolation

Table 4 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

DIETARY RISK FROM FOOD AND WATER			
	POPULATION	ESTIMATED RISK % of ACCEPTABLE DAILY INTAKE (ADI)	
		Food Only	Food and Water
Refined chronic non-cancer dietary risk **ADI = 0.25 mg/kg bw/day** **Estimated chronic drinking water concentration = 2.8 μg a.i./L**	**All infants < 1 year**	0.2	0.2
	Children 1–2 years	1.5	1.6
	Children 3–5 years	1.1	1.1
	Children 6–12 years	0.4	0.5
	Youth 13–19 years	0.2	0.2
	Adults 20–49 years	0.2	0.2
	Adults 50+ years	0.2	0.3
	Females 13–49 years	0.2	0.2
	Total population	0.3	0.3

Table 5 Alternative modes of action fungicides registered to control powdery mildew (*Uncinula necator*) on grapes.

Active Ingredient	Fungicide Group
Copper (copper oxychloride, tri-basic copper sulphate)	M
Dinocap	M
Sulphur	M
Calcium polysiphide	M
Myclobutanil	3
Boscalid	7
Kresoxim-methyl	11
Trifloxystrobin	11
Potassium bicarbonate	NC
Bacillus subtilis strain QST713	44

Table 6 Use (label) Claims Proposed by Applicant and Whether Acceptable or Unsupported

Proposed use claim	Supported / Unsupported
To control powdery mildew (*Uncinula necator*) in grapes, Vivando SC Fungicide should be applied at 0.750 – 1.12 L per hectare (224 – 336 g active ingredient (a.i.) per hectare) up to six times at 14–21 day intervals. The first application should be made at bud break prior to the onset of disease. The shorter interval should be used under conditions conducive to high disease pressure. Under conditions of very rapid growth, use the shorter application interval to ensure new growth is adequately protected.	Supported at 0.75 L/ha.

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

Table 1 Differences Between MRLs in Canada and in Other Jurisdictions

Please refer to Evaluation Report ERC2011-10, *Metrafenone* for the proposed MRLs for metrafenone.

References

A. List of Studies/Information Submitted by Registrant

1.0 Human and Animal Health

PMRA Document Number	Reference
2179988	2012, BASF response to Deficiency letter dated Jan 27 2012, DACO: 4.8
2179989	2010, BAS 560 F (Metrafenone) - Immunotoxicity study in female Wistar rats - Administration via the diet for 4 weeks, DACO: 4.8(B)
2269124	2013, BASF response to Deficiency letter dated Jan 3 2013, DACO: 4.8
2269125	2013, Elisa to Measure SRBC Specific Serum IgM: Method and Data Evaluation, DACO: 4.8(B)
2104355	2010, Extractability of BAS 560 F residues in selected solvent systems: A summary of results from the on-going metabolism study (BASF study no. 353807), DACO: 7.2.1
2104356	2011, Response to PMRA conditions of Registration as noted in the Section 12 Notice: Additional Information Required to Fulfill the Terms and Conditions for Conditional Registration, DACO: 7.2.1, 7.2.2
2104357	2010, Metrafenone (BAS 560 F): Validation of the multi-residue enforcement method QuEChERS for the determination of residues in plant matrices using LC/MS/MS, DACO: 7.2.1
2104358	2011, Independent laboratory validation of multi-method QuEChERS for the determination of Metrafenone (BAS 560 F) in foodstuffs of plant origin, DACO: 7.2.2
2179884	2010, Metabolism of 14C-BAS 560 F in cucumber, DACO: 7.2.1, 7.2.2
2179886	2012, Consumer safety Response to Deficiencies listed in PMRA Letter of January 27th 2012, DACO: 7.2.1, 7.2.2
2266393	2011, Extractability of BAS 560 F residues in cucumbers according to the multimethod (QuEChERS), DACO: 7.2.2
2266396	2011, Independent laboratory validation of multi-method QuEChERS for the determination of Metrafenone (BAS 560 F) in foodstuffs of plant origin (Including amendment no. 1 and amendment no. 2), DACO: 7.2.3

2.0 Environment

1620223	2002, BAS 560 F (AC 375839): Aerobic Transformation in Water-Sediment Systems (Including Amendment #1). BASF Study No.: E-99-003, Report No.: ENV 01-014/ENV 01-014.01 and Registration Document No.: 2002/7011484, DACO 8.2.3.5.2

2104360 2011, Response to PMRA Section 12 Notice Request for Additional Information for the Study Entitled "BAS 560 F (AC 375839): Aerobic Transformation in Water-Sediment Systems" Required to Fulfill the Terms and Conditions for Conditional Registration of Metrafenone under Registration No. 29764 (Application No. 2008-2850; PMRA No. 1931139). BASF Study No.: E-99-003, BASF Report No.: ENV 01-014 and ENV 01-014.01 and Registration Document No.: 2002/7011484, DACO 8.2.3.5.2, 8.2.3.5.4

3.0 Value

1620675 2008, Metrafenone 300 SC Fungicide (metrafenone) (BAS 560) Grapes (*Vitis* spp.) for the control of powdery mildew (*Uncinula necator*), N.A, MRID: N.A, DACO: 10.1,10.2.1,10.2.2,10.2.3.1,10.2.3.2(D),10.3.1,10.3.2,10.4,10.5.1,10.5.2,10.5.3

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

Payá P, Anastassiades M, Mack D, Sigalova I, Tasdelen B, Oliva J, and Barba A. (November 2007). "Analysis of pesticide residues using the Quick Easy Cheap Effective Rugged and Safe (QuEChERS) pesticide multiresidue method in combination with gas and liquid chromatography and tandem mass spectrometric detection". *Anal Bioanal Chem* **389** (6): 1697–714. doi:10.1007/s00216-007-1610-7. PMID 17909760.